

WHAT IS CLAIMED IS:

5 1. A DNA segment comprising an isolated gene encoding a modified retinoblastoma tumor suppressor protein other than pRB⁹⁴, said modified retinoblastoma tumor suppressor protein comprising an N-terminal modification.

10 2. The DNA segment of claim 1, wherein said gene encodes a modified retinoblastoma tumor suppressor protein comprising an N-terminal region that comprises a first sequence region from which at least one amino acid has been deleted.

15 3. The DNA segment of claim 2, wherein at least two amino acids have been deleted from said first sequence region.

20 4. The DNA segment of claim 3, wherein at least about 25 amino acids have been deleted from said first sequence region.

25 5. The DNA segment of claim 4, wherein at least about 100 amino acids have been deleted from said first sequence region.

30 6. The DNA segment of claim 5, wherein at least about 150 amino acids have been deleted from said first sequence region.

7. The DNA segment of claim 6, wherein at least about 300 amino acids have been deleted from said first sequence region.

8. The DNA segment of claim 2, wherein said first sequence region is located:

- 5
- a) between about amino acid 1 and about amino acid 50;
- b) between about amino acid 51 and about amino acid 100;
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- c) between about amino acid 101 and about amino acid 150;
- d) between about amino acid 151 and about amino acid 200;
- e) between about amino acid 201 and about amino acid 250;
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- f) between about amino acid 251 and about amino acid 300;
- g) between about amino acid 1 and about amino acid 100;
- h) between about amino acid 51 and about amino acid 150;
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- i) between about amino acid 101 and about amino acid 200;
- j) between about amino acid 151 and about amino acid 250;
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- k) between about amino acid 201 and about amino acid 300;
- l) between about amino acid 1 and about amino acid 150;
- m) between about amino acid 51 and about amino acid 200;
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n) between about amino acid 101 and about amino acid 250;

o) between about amino acid 151 and about amino acid 300;

5 p) between about amino acid 1 and about amino acid 200;

q) between about amino acid 51 and about amino acid 250;

10 r) between about amino acid 101 and about amino acid 300;

s) between about amino acid 1 and about amino acid 250;

t) between about amino acid 51 and about amino acid 300; or

15 u) between about amino acid 1 and about amino acid 300.

9. The DNA segment of claim 2, wherein:

20 a) about amino acid 2 through about amino acid 34 have been deleted from said first sequence region;

b) about amino acid 2 through about amino acid 55 have been deleted from said first sequence region;

25 c) about amino acid 2 through about amino acid 78 have been deleted from said first sequence region;

30 d) about amino acid 2 through about amino acid 97 have been deleted from said first sequence region;

e) about amino acid 2 through about amino acid 148 have been deleted from said first sequence region;

5 f) about amino acid 31 through about amino acid 107 have been deleted from said first sequence region;

g) about amino acid 77 through about amino acid 107 have been deleted from said first sequence region;

10 h) about amino acid 111 through about amino acid 181 have been deleted from said first sequence region;

15 i) about amino acid 111 through about amino acid 241 have been deleted from said first sequence region;

j) about amino acid 181 through about amino acid 241 have been deleted from said first sequence region; or

20 k) about amino acid 242 through about amino acid 300 have been deleted from said first sequence region.

25 10. The DNA segment of claim 2, wherein said N-terminal region of said modified retinoblastoma tumor suppressor protein further comprises a second sequence region from which at least one amino acid has been deleted.

30 11. The DNA segment of claim 10, wherein about amino acid 2 through about amino acid 34, and about amino acid 76 through about amino acid 112 have been deleted.

12. The DNA segment of claim 10, wherein about amino acid 2 through about amino acid 55, and about amino acid 76 through about amino acid 112 have been deleted.

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13. The DNA segment of claim 1, wherein said gene encodes a modified retinoblastoma tumor suppressor protein comprising at least a first N-terminal mutation, and wherein said modified retinoblastoma tumor suppressor protein has an increased biological activity in comparison to the biological activity of the corresponding wild-type retinoblastoma tumor suppressor protein.

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14. The DNA segment of claim 13, wherein said gene encodes a modified retinoblastoma tumor suppressor protein comprising a mutation at position 111.

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15. The DNA segment of claim 14, wherein said modified retinoblastoma tumor suppressor protein comprises glycine at position 111 in place of aspartic acid.

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16. The DNA segment of claim 13, wherein said modified retinoblastoma tumor suppressor protein comprises at least a second N-terminal mutation.

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17. The DNA segment of claim 16, wherein said gene encodes a modified retinoblastoma tumor suppressor protein comprising a mutation at position 111 and a mutation at position 112.

18. The DNA segment of claim 17, wherein said modified retinoblastoma tumor suppressor protein comprises glycine at position 111 in place of aspartic acid, and aspartic acid at position 112 in place of glutamic acid.

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19. The DNA segment of claim 1, wherein said gene encodes a modified retinoblastoma tumor suppressor protein comprising an N-terminal region from which at least one amino acid has been deleted, and which contains at least one amino acid mutation.

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20. The DNA segment of claim 2, wherein said gene encodes a modified retinoblastoma tumor suppressor protein that comprises at least the C-terminal amino acid sequence from about position 370 to about position 928 of SEQ ID NO:2.

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21. The DNA segment of claim 2, wherein said gene encodes a modified retinoblastoma tumor suppressor protein comprising the contiguous amino acid sequence of SEQ ID NO:29; SEQ ID NO:31; SEQ ID NO:33; SEQ ID NO:35; SEQ ID NO:37; SEQ ID NO:39; SEQ ID NO:41; SEQ ID NO:43; SEQ ID NO:45; SEQ ID NO:47; SEQ ID NO:49; or SEQ ID NO:51.

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22. The DNA segment of claim 2, wherein said gene comprises the contiguous nucleic acid sequence from between position 7 and position 2691 of SEQ ID NO:28; from between position 7 and position 2628 of SEQ ID NO:30; from between position 7 and position 2559 of SEQ ID NO:32; from between position 7 and position 2502 of SEQ ID NO:34; from between position 7 and position 2349 of SEQ ID NO:36; from between position 7 and position 2559 of SEQ ID NO:38; from between position 7 and position 2697 of SEQ ID NO:40; from between position 7 and position 2583 of SEQ ID NO:42; from between position 7 and position 2397 of SEQ ID NO:44; from between position 7 and position 2613 of SEQ ID NO:46; from between position 7

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and position 2619 of SEQ ID NO:48; or from between position 7 and position 2790 of SEQ ID NO:50.

5 23. The DNA segment of claim 1, operationally positioned under the control of a promoter.

24. The DNA segment of claim 23, further defined as a recombinant vector.

10 25. The DNA segment of claim 24, wherein said recombinant vector is comprised within an adenoviral vector.

15 26. The DNA segment of claim 25, wherein said adenoviral vector is comprised within a recombinant adenovirus.

20 27. The DNA segment of claim 1, comprised within a host cell.

28. The DNA segment of claim 27, wherein said host cell is a eukaryotic cell.

25 29. The DNA segment of claim 28, wherein said host cell is a human cell.

30 30. The DNA segment of claim 28, wherein said host cell is a tumor cell.

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31. The DNA segment of claim 28, wherein said host cell is comprised within an animal.

32. The DNA segment of claim 31, wherein said animal is a human subject.

33. The DNA segment of claim 1, dispersed in a pharmaceutically acceptable excipient.

34. The DNA segment of claim 1, wherein said modified retinoblastoma tumor suppressor protein is characterized as:

a) comprising an N-terminal region that comprises at least a first sequence region from which at least one amino acid has been deleted, and wherein said modified retinoblastoma tumor suppressor protein has a biological activity at least about equivalent to the biological activity of the corresponding wild-type retinoblastoma tumor suppressor protein; or

b) comprising an N-terminal region that comprises a first sequence region comprising at least one mutation, and wherein said modified retinoblastoma tumor suppressor protein has an increased biological activity in comparison to the biological activity of the corresponding wild-type retinoblastoma tumor suppressor protein.

35. A modified retinoblastoma tumor suppressor protein other than pRB⁹⁴, said modified retinoblastoma tumor suppressor protein comprising an N-terminal modification, wherein said modified retinoblastoma tumor suppressor protein has a biological activity at least about equivalent to the biological activity of the corresponding wild-type retinoblastoma tumor suppressor protein.

36. A recombinant host cell comprising a DNA segment comprising an isolated gene encoding a modified retinoblastoma tumor suppressor protein other than pRB⁹⁴, said modified
5 retinoblastoma tumor suppressor protein comprising an N-terminal modification.

37. The recombinant host cell of claim 36, wherein said host cell is a tumor cell.

10 38. A method of inhibiting cellular proliferation, comprising contacting a cell with an effective inhibitory amount of a first modified retinoblastoma tumor suppressor protein other than pRB⁹⁴, said modified retinoblastoma tumor suppressor protein comprising an N-terminal modification.

15 39. The method of claim 38, wherein said cell is contacted with said first modified retinoblastoma tumor suppressor protein by providing to said cell a DNA segment that expresses said first modified retinoblastoma tumor suppressor protein in said cell.

20 40. The method of claim 38, wherein said cell is located within an animal and said first modified retinoblastoma tumor suppressor protein, or a gene encoding said modified retinoblastoma tumor suppressor protein, is administered to said animal in a pharmaceutically
25 acceptable vehicle.

30 41. The method of claim 38, wherein said cell is contacted with a modified retinoblastoma tumor suppressor protein and a p53 tumor suppressor protein in a combined amount effective to inhibit cellular proliferation in said cell.

42. A method of inhibiting cellular proliferation, comprising contacting a cell with a retinoblastoma protein and a p53 protein in a combined amount effective to inhibit cellular proliferation in said cell.

43. A method of treating cancer, comprising administering to an animal with cancer a pharmaceutically acceptable composition comprising a biologically effective inhibitory amount of a first modified retinoblastoma tumor suppressor protein, other than pRB⁹⁴, that comprises an N-terminal modification.

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